Remarks

This amendment amends the Title of the Invention and the specification, and adds new claim 84. Support for the amendments can be found in the original specification and claims as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Applicants' Attorney hereby states that the amendments in the specification and the changes made in the Sequence Listing do not include new matter. The Amendment corrects a formal matter without changing the scope of the claims.

The Sequence Listing has been amended by correcting the numbering of the amino acid residues in SEQ ID NO:1 and SEQ ID NO:2 to start from the glycine residue instead of the methionine residue. Support for this amendment can be found in Figure 1 originally filed. Applicants' Attorney has amended the specification only to direct the entry of this Substitute Sequence Listing at the end of the application.

In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter.

In accordance with 37 C.F.R. § 1.825(b), the paper copy of the Substitute Sequence Listing and the computer-readable copy of the Substitute Sequence Listing submitted herewith are the same.

New claim 84 is sought to be added. Support for claim 84 can be found at page 8, lines 8-12 of the specification as originally filed.

Upon entry of the foregoing amendment, claims 39, 41, 42, and 48-84 are pending in the application, with claims 39, 41, and 42 being the independent claim. As such, no new matter has been introduced into the captioned application.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I Election/Restriction

Applicants note that the Examiner has made the requirement for restriction final and withdrawn claims 41, 42, and 48-83 from further consideration as far as they encompass methods other than a method for stimulating cell division. Claims 39 and 54-81 are under consideration as far as they read on the elected invention.

II Priority

The Examiner has requested the application be amended by including the current status of all nonprovisional parent applications referenced. Applicants have amended the first paragraph of the specification by inserting the current status of the parent application No. 09/220,077.

III Specification

The Examiner has objected to the title of the invention as not being descriptive. Applicants have amended the title by inserting the phrase --Methods of Using-- in the beginning of the title as suggested by the Examiner. Applicants have also amended the title by inserting the

specific amino acid positions that may be mutated. It is respectfully submitted that this objection has been overcome and should be withdrawn.

IV Claim Objections

The Examiner has objected to claims 54-61 and 70-74 as being directed to non-elected subject-matter and depend from non-elected claims. Upon the indication of allowable claims, Applicants proffer the correction of these claims such that they are not directed to non-elected subject-matter or depend from non-elected claims.

V Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 39 and 54-81 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of stimulating cell division by administering a mutein of bFGF comprising the substitution of position 89 with either alanine or tyrosine and the substitution of either of positions 101 or 137 with alanine, allegedly does not reasonably provide enablement for a method utilizing a mutein with a substitution of those positions with any neutral amino acid or hydrophobic amino acid. The Examiner further alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The enablement requirement of § 112, first paragraph, ensures that one skilled in the art will be able to make and use the invention. Further, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. M.P.E.P. § 2164.01. "[A] considerable amount of experimentation is permissible, if it is merely routine,

or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The Examiner argues as follows:

> [A]lanine in the only amino acid which has been substituted as [*sic*] all three positions and tyrosine has only been substituted at position 89 and one of ordinary skill in the art would not find these substitutions predictive of all amino acids which are encompassed by the claim limitations of neutral or hydrophobic amino acids.

At page 6, lines 14-17, of the Office Action.

Further, the Examiner asserts that

> [O]ne cannot predict from the substitution of alanine at these positions what biological property will be possessed by the other substitutions.

At page 7, lines 17-19, of the Office Action.

According to the Examiner, the claims are not commensurate in scope with the enabling disclosure because

> unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

At page 8, lines 8-12, of the Office Action.

Applicants respectfully disagree. Applicants submit herewith a copy of the Declaration from Barry A. Springer, Ph.D. previously filed on October 25, 2000 in connection with the prosecution of the parent application Serial No. 09/220,077. It is respectfully submitted that the

enablement of claims 39 and 54-81 is supported by the specification as filed and publications available at the time the above-captioned application was filed for at least the following reasons.

There is ample evidence in the literature that usually small, minor local changes in a protein do *not* change the activity or the overall structure of the protein. For example, Watson *et al.* describe that single amino acid substitutions usually do not alter enzyme activity (See ¶8, Springer Decl.). This has also been acknowledged at the U.S. Patent and Trademark Office, Board of Appeals and Interferences. See *Ex parte Maizel*, 27 U.S.P.Q. 2d. 1662 (B.P.A.I. 1993). Furthermore, Bowie *et al.* has examined amino acid substitutions within a protein and the likelihood that such mutations will affect biological activity. The authors reported that proteins are surprisingly tolerant of amino acid substitutions, and that the choice of substitution at a given amino acid residue depends, in part, on the location of the residue within the protein's three dimensional structure (See ¶8, Springer Decl.). Furthermore, Cunningham *et al.* evidences that when the mutagenesis does not change the structure of the protein, the function of the protein is conserved (See ¶8 and Exhibit 7 of Springer Decl.).

In the present application, it has been discovered that the replacement of one or more of the amino acids glutamate at position 89, aspartate at position 101 or leucine at position 137 with a neutral and/or hydrophobic amino acid provides a mutein with improved mitogenic agonist activity. These positions, glutamate 89, aspartate 101 and leucine 137, are on the surface of the protein (See ¶6, Springer Decl.). Surface amino acid positions are more tolerant of substitution than buried amino acid positions (See ¶7, Springer Decl.). Thus, it can be reasonably expected that substitutions on the surface of the protein with a neutral and/or hydrophobic amino acid are accommodated and are conservative of structure and, thus, of function. Therefore, it can be reasonably expected that the substitution of alanine at one or more of the positions glutamate 89,

aspartate 101 and leucine 137 with another neutral amino acid and/or a hydrophobic amino acid will provide the biological effect seen by alanine substitutions at those positions (See ¶13, Springer Decl.). It follows that it can be reasonably expected that a mutein substituted at one or more of the amino acids glutamate at position 89, aspartate at position 101 or leucine at position 137 with a neutral and/or hydrophobic amino acid can be used in a method of stimulating cell division as claimed in claim 39 based on the substitutions with alanine at those positions.

Applicants have shown in the instant specification that substitutions at any of these surface amino acid positions with alanine or at position 89 with tyrosine do not destroy the protein structure but protect it, because the protein function is preserved. Hence, proteins with mitogenic agonist function are provided. Moreover, Applicants have shown in the application as filed that the substitutions not only provide a conserved mitogenic agonist function, but an improved mitogenic agonist function. Alanine and tyrosine are predictive of other neutral and/or hydrophobic amino acids because one of ordinary skill in the art can reasonably extrapolate from the substitutions with alanine and tyrosine to substitutions with other neutral and/or hydrophobic amino acids. This is evidenced by Dr. Springer in his Declaration.

Dr. Springer's Declaration provides evidence that 1) glutamate at position 89, aspartate at position 101 or leucine at position 137 were known in the art to be located on the surface of the human bFGF (See ¶6, Springer Decl.), and that 2) neutral and/or hydrophobic substitutions on the surface of the protein are accommodated and do not destroy the structure of the protein (See ¶5, Springer Decl.), and, therefore, 3) the function of the protein is not changed. Hence, it would have been reasonably expected at the time the application was filed that substitutions at glutamate 89, aspartate 101, and leucine 137 with a neutral and/or hydrophobic amino acids protect the structure of human bFGF and, thus, provide a protein with mitogenic agonist, or even

improved mitogenic agonist, function. Furthermore, Dr. Springer's Declaration provides evidence that the art was predictable at the time of the application was filed. The state of the art was advanced and the level of ordinary skill was very high at the time the application was filed. Therefore, only routine experimentation would have been required for the preparation and screening of muteins at the time the application was filed (See ¶13, Springer Decl.). Thus, it would have been reasonably expected at the time the application was filed that a mutein substituted at one or more of the amino acids glutamate at position 89, aspartate at position 101 or leucine at position 137 with a neutral and/or hydrophobic amino acid can be used in a method of stimulating cell division as claimed in claim 39.

The Examiner asserts that

> [t]he instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing a protein which has the same biological activity as the alanine substitutions.

At page 8, lines 16-19, of the Office Action.

Applicants respectfully disagree. It is respectfully submitted that non-naturally occurring analogs of neutral and hydrophobic amino acids as defined at page 8, lines 8-12, of the specification can be prepared by methods known in the art, or they are commercially available, e.g., by Peptech Corporation. Further, the muteins of human bFGF, or biologically active peptides thereof, according to the present invention can be prepared by simple mutagenesis. At the time the above-captioned application was filed, plenty of guidance on protein mutagenesis was available to protein biochemists of ordinary skill. For example, methods described at page 9, lines 11-16, and at page 10, lines 3-11, of the specification and in Example 1 can be used. This is supported by Dr. Springer's Declaration (See ¶11, Springer Decl.). As supported by case law, Applicants need not supply information that is well known in the art. See *In re Howarth*,

654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981); *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 U.S.P.Q.2d at 1005; and *In re Brebner*, 455 F.2d 1402, 173 U.S.P.Q. 169 (C.C.P.A. 1972). Moreover, one of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. See *In re Howarth*, 654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981).

Further, mitogenic agonist activity of the bFGF mutant proteins according to the invention can be determined by simply comparing mutein and wild-type bFGF stimulation of fibroblast growth. The method of screening is described in detail in Example 3 of the specification. A person of ordinary skill at the time the above-captioned application was filed would have been able without undue experimentation to follow the guidance of the specification and determine whether a mutein has improved mitogenic agonist activity. This is also supported by Dr. Springer's Declaration (See ¶12, Springer Decl.).

Thus, contrary to the Examiner's arguments, the instant specification provides a description of a repeatable process for preparing the muteins of the present invention in Example 1, and a repeatable process for testing their mitogenic activity in Example 3. Example 1 describes a repeatable process for substitution with both a neutral amino acid, alanine, and a hydrophobic amino acid, tyrosine. The process of testing described in Example 3 was used in three different cell lines, i.e., Swiss 3T3, NIH 3T3, and Balb/c 3T3, and the results remained consistent for all three cell lines tested. Moreover, Table 1 of the specification shows by the number of experiments conducted for each tested mutein that the test procedure is repeatable.

Furthermore, the specification as filed provides suitable concentrations of muteins for stimulating cell division *in vitro* at page 17, line 31 through page 18, line 5, and *in vivo* at page 19, line 31 through page 20, line 5.

According to M.P.E.P. § 2164.01(b),

> [a]s long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. . . . Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112.

Applicants respectfully submit that the instant specification has met this burden.

It is respectfully submitted that the claims are not unduly broad as alleged by the Examiner. They are in fact limited to utilizing muteins having conservative changes at only three surface positions. The claims are not drawn to utilizing muteins having all substitutions at three surface positions, and they are not drawn to utilizing muteins having conservative substitutions at all positions. None of *In re Fisher*, *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* and *Genentech Inc. v. Novo Nordisk A/S* is applicable. The issue in *In re Fisher* was whether an open-ended recitation in a claim rendered the claim too broad, and the present claims do not include any open-ended recitation. *Amgen* relates to the breadth of a single means claim, and the present claims do not include any single means claim. *Genentech* does not deal with the breadth of the claims.

The instant specification, the Springer Declaration and the references cited thereon support the predictability of this area of the art. It is respectfully submitted that the Examiner has not provided adequate reasons to establish that a person skilled in the art could not make and use muteins of the present invention other than the ones expressly exemplified without undue experimentation. In fact, the Examiner has not provided any factual basis on which it can be concluded that one skilled in the art would not be able to stimulate cell division by contacting cells with muteins of human bFGF according to the invention other than those expressly exemplified. Applicants' conclusions are supported by evidence. Dr. Springer's Declaration is

that evidence. Applicants respectfully submit that a "declaration or affidavit is, itself, evidence that must be considered." See M.P.E.P. § 2164.05. Furthermore, Dr. Springer's Declaration cites several references, i.e., provides factual evidence, to support the conclusions.

Applicants wish to point out that claims to muteins recited in claims 61-69 have been earlier issued in the parent patent No. 6,274,712 B1.

In view of the above, reconsideration and withdrawal of the rejection of claims 39 and 54-81 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

VI Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 39 and 54-81 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner alleges that the claims are indefinite for the recitation of mutein. The Examiner's arguments are as follows:

> The instant claims encompass the substitution of position 137 with a hydrophobic amino acid, which includes the naturally occurring amino acid leucine at this position. It is not clear how the substitution of leucine at position 137 with leucine would provide for a mutein, wherein the specification describes a mutein as having an altered property, structural or functional.

Applicants respectfully disagree. It would be clear for a person skilled in the art wishing to substitute leucine at position 137 with a hydrophobic amino acid in order to get a mutein having altered property, not to select leucine for the substitution but another hydrophobic amino acid. The recitation of the word "mutein" in claim 39 makes it clear that the substitution of leucine at position 137 with leucine is not intended to be encompassed by the claims.

Further, the Examiner alleges that the recitation "comprising the substitution of a neutral and/or hydrophobic amino acid for one or more of the following" is confusing because, according to the Examiner, it seems to imply that two amino acids could replace one of the recited amino acids. Applicants respectfully disagree. It is clear from the specification at page 8, lines 13-18, that claim 39 encompass replacement of one amino acid with one amino acid.

In view of the above, reconsideration and withdrawal of the rejection of claims 39 and 54-81 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

In the Title of the Invention:

The title of the invention has been amended as follows:

Methods of Using Analogs of Human basic Fibroblast Growth Factor Mutated at One or More of the Positions Glutamate 89, Aspartate 101 or Leucine 137

In the Specification:

The first paragraph has been amended as follows:

This is a divisional of U.S. Patent Application Serial No. 09/220,077, filed December 23, 1998, now U.S. Patent No. 6,274,712 B1, which claims the benefit, under 35 U.S.C. § 119(e), of the earlier filing date of U.S. Provisional Application, Appl. No. 60/068,667, filed on December 23, 1997. The entirety of each of these applications is incorporated by reference herein.

In the Claims:

New claims 84 has been added.